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(12) (19) (CA) **Demande-Application**

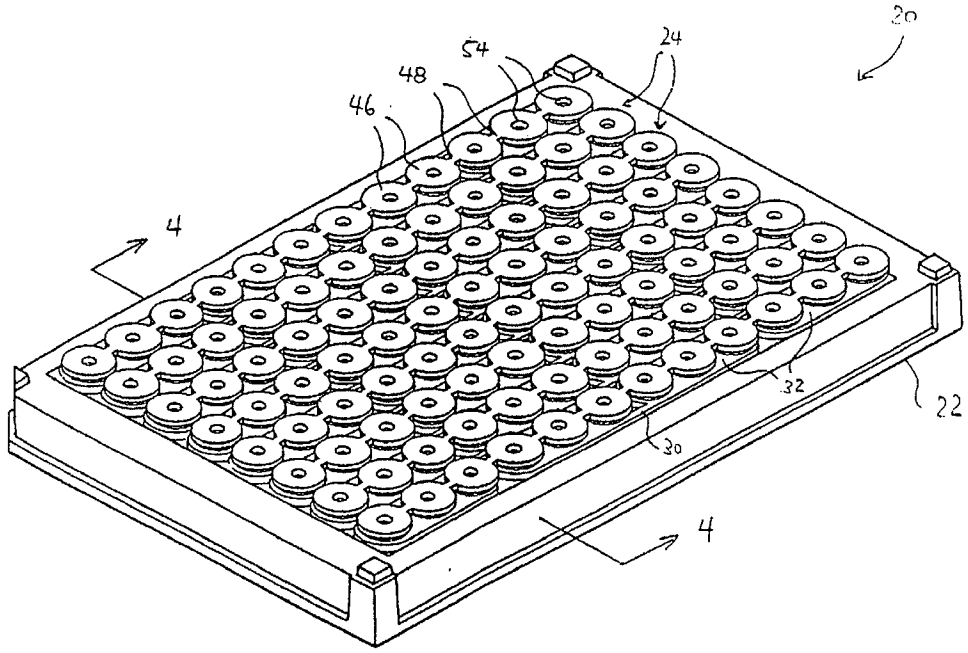
(21) (A1) **2,215,561**
(22) 1997/09/15
(43) 1998/03/26

(72) LAWRENCE, Nathan P., US
(71) Becton, Dickinson and Company, US

(51) Int.Cl.[6] C12Q 1/00, C12Q 1/68, G01N 33/50, C12M 1/40, B01L 3/00
(30) 1996/09/26 (08/721,386) US

(54) **PUITS D'ECHANTILLONS COUVERTS POUR ESSAIS D'ACIDES NUCLEIQUES ET IMMUNO-ESSAIS**

(54) **COVERED SAMPLE WELL FOR USE IN NUCLEIC ACID ASSAYS AND IMMUNOASSAYS**



(57) Puits d'échantillons pour mettre en oeuvre une méthode biologique ou chimique, comme un essai d'acide nucléique ou un immuno-essai avec un échantillon liquide. Le puits comporte un capuchon avec une ouverture restreinte, suffisante pour recevoir l'extrémité distale du bout d'une pipette jetable. Le bout de la pipette est inséré initialement dans l'ouverture pour introduire un échantillon liquide dans le puits, et il demeure dans celle-ci pendant que l'échantillon réagit avec un réactif se trouvant dans le puits. De cette façon, le bout de la pipette bouche complètement le puits pendant la réaction, ce qui réduit les pertes d'échantillon par évaporation et empêche la contamination croisée avec les échantillons des puits voisins. Les puits peuvent également être constitués de matériaux divers qui jouent différents rôles dans le processus biologique ou chimique, ce qui permet de constituer des montages de groupes différents de puits, correspondant à des modes d'essai différents.

(57) An improved sample well is provided for carrying out a biological or chemical process, such as a nucleic acid assay or an immunoassay, on a liquid sample. The sample well includes a cap with a restricted aperture sufficient in size to receive the distal end of a disposable pipette tip. The pipette tip is initially inserted into the aperture to introduce a liquid sample into the sample well, and is allowed to remain within the aperture while the sample reacts with a reagent contained within the sample well. In this way, the pipette tip effectively closes off the sample well while the reaction is taking place, thereby reducing evaporative loss of the sample and avoiding cross-contamination with samples contained in adjacent sample wells. The sample wells may also be constructed of, or include therein, different materials which perform different functions in the biological or chemical process, thereby permitting assembly of different groups of sample wells for different assay formats.

ABSTRACT OF THE DISCLOSURE

An improved sample well is provided for carrying out a biological or chemical process, such as a nucleic acid assay or an immunoassay, on a liquid sample. The sample well includes a cap with a restricted aperture sufficient in size to receive the distal end of a disposable pipette tip. The pipette tip is initially inserted into the aperture to introduce a liquid sample into the sample well, and is allowed to remain within the aperture while the sample reacts with a reagent contained within the sample well. In this way, the pipette tip effectively closes off the sample well while the reaction is taking place, thereby reducing evaporative loss of the sample and avoiding cross-contamination with samples contained in adjacent sample wells. The sample wells may also be constructed of, or include therein, different materials which perform different functions in the biological or chemical process, thereby permitting assembly of different groups of sample wells for different assay formats.

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COVERED SAMPLE WELL FOR USE IN NUCLEIC ACID ASSAYS AND IMMUNOASSAYS

Cross-Reference to Related Applications

Related subject matter is disclosed and claimed in a co-pending patent application of Hugh V. Cottingham et al, Serial No. 08/470,326, filed June 6, 1995, for "Nucleic Acid Amplification Method and Apparatus"; in a co-pending patent application of Michael L. Lamos et al, Serial No. 08/410,245, filed on March 24, 1995, and entitled "Pipette Tip"; in a co-pending patent application of Allen S. Reichler et al, Serial No. 08/409,821, filed on March 24, 1995 and entitled "System for Nucleic Acid Based Diagnostic Assay"; in a co-pending patent application of Allen S. Reichler et al, Serial No. 08/409,405, filed on March 24, 1995 and entitled "Nucleic Acid Amplification Method and Apparatus"; and in a co-pending patent application of Hugh V. Cottingham et al, Serial No. 08/213,304, filed on March 14, 1994 and entitled "Nucleic Acid Amplification Method and Apparatus", the disclosures of all of said applications being expressly incorporated herein by reference.

Field of the Invention

The present invention relates to an improved sample well that is useful for carrying out a biological or chemical process (such as a nucleic acid assay or an immunoassay) on a liquid sample, and is particularly concerned with a covered sample well that reduces sample evaporation and avoids cross-contamination between different samples when used in conjunction with an automated pipetting apparatus, which sample well may be made of, or coated with, different materials to permit its utilization for different aspects of a biological or chemical process when used with other sample wells in a plate or kit format.

Background of the Invention

Biological processes are often utilized in clinical diagnostics assays. However, the steps of the processes frequently are conducted in different areas of the laboratory and/or in different vessels or containers, thereby necessitating transport of biological samples and reagents and giving rise to increased risk of contamination of other clinical samples.

The risk of contamination is of particular concern when the process includes nucleic acid amplification reactions such as Strand Displacement Amplification (SDA), thermophilic Strand Displacement Amplification (tSDA), or Polymerase Chain Reaction (PCR), which are capable of multiplying a single strand of nucleic acid (target nucleic acid) into millions of copies (amplicons). While of tremendous potential utility in the clinical diagnostic laboratory, nucleic acid amplification reactions can, however, easily become contaminated with the amplification products (amplicons) of previous amplification reactions. Such contaminating amplicons can in turn contaminate new samples entering the lab, leading to a false positive indication of the substrate to be detected in the contaminated sample (e.g., an incorrect diagnosis). The problem of amplicon contamination has led to the development of a number of decontamination techniques. In order to be effective, these decontamination techniques generally require that the decontamination step of the process occur prior to the amplification step, thereby greatly decreasing the possibility that a contaminating amplicon will be recognized as target nucleic acid during the amplification step.

Decontamination reagents and amplification reagents are often not compatible with each other and may require their own reaction conditions. Sometimes, if the reagents for decontamination and amplification are combined, they inactivate each other.

In a co-pending, commonly-assigned patent application of Hugh V. Cottingham et al, Serial No. 08/213,304, filed on March 14, 1994 and entitled "Nucleic Acid Amplification Method and Apparatus", an apparatus is described which reduces or eliminates these problems by allowing decontamination and amplification to be carried out within the confines of a single module. In general, the disclosed module includes a sample well for the introduction and removal of a liquid biological sample, at least one reaction chamber in fluid communication with the sample well, a pneumatic chamber in pneumatic communication with the reaction chamber and sample well, and a pneumatic port in the pneumatic chamber for allowing connection of the apparatus to a pneumatic

aspiration/dispensing means. Operation of the pneumatic aspiration/dispensing means causes the liquid biological sample to flow between the sample well and the reaction chamber in a controlled manner. In a preferred embodiment, the module is generally elongate in shape, with the sample well and pneumatic port at opposite ends and the reaction chamber therebetween. Reagents necessary for the decontamination and amplification reactions are affixed to separate, discrete locations within the reaction chamber, and the liquid biological sample is moved between these locations by operating the pneumatic aspiration/dispensing means.

The module described in Serial No. 08/213,304 is particularly suited for use in an automated processing apparatus, since the necessary liquid transfers and sample movements can be carried out automatically using a robotic pipetting system. The robotic pipetting system can be of a conventional type, although modifications are necessary (including the provision of a specialized pneumatic pipette tip) to allow pneumatic aspiration and dispensing to be carried out at the pneumatic port of the module. An example of such an automated processing apparatus is disclosed in a co-pending, commonly-assigned patent application of Allen S. Reichler et al, Serial No. 08/409,821, filed on March 24, 1995 and entitled "System for Nucleic Acid Based Diagnostic Assay".

In the module described in Serial No. 08/213,304, liquid flow control means in the form of microchannels are used to control the flow of the liquid biological sample between the sample well and the reaction chamber, and, if more than one reaction chamber is provided, between the reaction chambers themselves. In addition to performing the desired liquid flow control function, the microchannels also reduce evaporation of the liquid biological sample from the module during the decontamination and amplification steps. Given the relatively small quantity of liquid biological sample used (typically about 55 microliters), the relatively high temperatures employed during certain portions of the process (up to 80° C) and the length of time required to complete the decontamination and amplification reactions (approximately 1 and 2 hours, respectively), evaporation of the sample can be a significant problem. In extreme cases, the extent of evaporation may be such that there is an insufficient amount of liquid biological sample remaining to be recovered and assayed after the decontamination and amplification steps are complete. With the use of properly dimensioned microchannels, however, the problem of evaporative loss can be kept under control.

Unfortunately, despite their advantages, microchannels require rather precise dimensional tolerances and are therefore difficult to fabricate. As disclosed in co-pending patent application Serial No. 08/213,304, flow control between successive reaction chambers is possible without the use of microchannels by causing the liquid biological sample to flow as a single undivided unit

(bolus) within the module. However, microchannels are still retained at both ends of the apparatus, in part to reduce evaporative loss through the sample well and pneumatic port.

A number of improvements to the module described above are described in a co-pending, commonly-assigned U.S. patent application of Allen S. Reichler et al, Serial No. 08/409,805, filed on March 24, 1995 and entitled "Nucleic Acid Amplification Method and Apparatus". Among these improvements are the use of a sample tower in fluid communication with the sample-receiving area of the module for reducing evaporation of the liquid biological sample through the sample port, and a pneumatic tower for reducing evaporation of the liquid biological sample through the pneumatic port at the opposite end of the module. The sample tower and pneumatic tower capture liquid vapors that are produced by the liquid biological sample while it is undergoing decontamination and amplification within the module, thereby producing humidity gradients that reduce the rate of evaporative loss from the module. The towers also serve to shroud the openings at either end of the module from ambient air currents, and to provide condensation surfaces that return liquid vapors to the module in the form of condensed droplets. By virtue of the sample tower and pneumatic tower, the need for microchannels within the apparatus to control evaporative loss is reduced.

Despite these improvements, the module described in co-pending application Serial No. 08/409,805 is still subject to a number of disadvantages and limitations. For example, although the sample tower and pneumatic tower are effective in reducing evaporative loss of the liquid biological sample, some loss still occurs since the sample port and pneumatic port are open while the decontamination and amplification reactions are occurring and thus provide an escape path for liquid vapors. A related problem is the release of liquid aerosols from the module, which can occur during automatic pipetting operations. When a number of modules are processed in close proximity to each other in an automated processing apparatus of the type disclosed in co-pending application Serial No. 08/409,821, aerosol formation can potentially result in cross-contamination between different samples. Other disadvantages of the module described in Serial No. 08/409,805 are that it is difficult to manufacture (due to its specialized configuration), and its dimensions, geometry and material must be carefully selected in order to allow for the desired bolus movement of the liquid sample within the reaction area of the module. The need for a pneumatic aspiration/dispensing means to control sample movement within the module is also undesirable, since it imposes additional requirements on the automated processing apparatus in which the module is used.

It is therefore an object of the present invention to provide an apparatus for performing a biological or chemical process, such as a nucleic acid assay or an immunoassay, in which problems

due to evaporative loss of the liquid sample are reduced or eliminated.

It is another object of the invention to provide an apparatus for performing a biological or chemical process, such as a nucleic acid assay or an immunoassay, in which the potential for cross-contamination between different liquid samples is reduced or eliminated, particularly when the samples are being processed simultaneously and in close proximity to each other in an automated processing apparatus.

It is a further object of the invention to provide an apparatus for performing a biological or chemical process which is simple and inexpensive to fabricate, and which is not constrained in terms of geometry, dimensions or material selection.

It is a still further object of the invention to provide an apparatus for performing a biological or chemical process, such as a nucleic acid assay or an immunoassay, which has a configuration similar to that of existing types of biological and chemical sample containers, and which can therefore be manufactured by methods similar to those currently employed.

It is a still further object of the invention to provide an apparatus for performing a biological or chemical process, such as a nucleic acid assay or an immunoassay, which is compatible with conventional types of automated pipetting systems and does not require the use of specialized pneumatic aspiration and dispensing devices to move the liquid sample from one reaction site to another.

It is a still further object of the invention to provide an apparatus for performing a biological or chemical process, such as a nucleic acid assay or an immunoassay, having different wells for different functions, such wells being available to be assembled in different configurations to provide a user with multiple options for assay configuration or kit manufacture.

Summary of the Invention

In accordance with the present invention, the foregoing disadvantages and limitations are avoided by carrying out a biological or chemical process, such as a nucleic acid assay or an immunoassay, in a covered or capped sample well that has a restricted aperture sufficient in size to receive the distal end of a disposable pipette tip. The pipette tip is initially inserted into the aperture to introduce a liquid sample into the sample well, and is allowed to remain within the aperture while the sample reacts with a reagent contained within the sample well. In this way, the pipette tip

effectively closes off the sample well while the reaction is taking place, thereby reducing evaporative loss of the sample and avoiding cross-contamination with samples contained in adjacent sample wells.

In one aspect, therefore, the present invention is directed to an apparatus for carrying out a biological or chemical process on a liquid sample. The apparatus comprises a sample well for receiving the liquid sample, with the sample well having an interior portion and a top opening communicating with the interior portion. A cap is receivable in the top opening of the sample well, and has a restricted aperture smaller than the top opening of the sample well for communicating with the interior portion of the sample well. A reagent is affixed within the interior portion of the sample well for reacting with the liquid sample. In a preferred embodiment of the invention, the reagent is one that is suitable for use in a nucleic acid assay and may comprise, for example, a dried nucleic acid decontamination reagent, a dried nucleic acid amplification reagent or an immobilized nucleic acid detection reagent. In other embodiments, the reagent may be one suited for use in a immunoassay, or one adapted for use in any other desired biological or chemical process.

In another aspect, the present invention is directed to a method for carrying out a biological or chemical process on a liquid sample. The method comprises the steps of drawing the liquid sample into a pipette tip, introducing a distal portion of the pipette tip into a sample well through a restricted aperture in the sample well, transferring a liquid sample from the pipette tip into the sample well, and carrying out a reaction on the liquid sample in the sample well while maintaining the distal portion of the pipette tip in the restricted aperture. Preferably, the outer surfaces of the pipette tip are brought into sufficiently close proximity with the edges of the aperture so that the pipette tip forms a closure for the aperture during the reaction. It is also preferred that the distal end of the pipette tip be brought into close proximity with the bottom of the sample well, so that the liquid sample can be drawn back into the pipette tip after the reaction is complete.

In a still further aspect, the present invention is directed to a kit for carrying out a nucleic acid assay on a liquid biological sample. The kit comprises a first plurality of sample wells containing dried nucleic acid decontamination reagents, a second plurality of sample wells containing dried nucleic acid amplification reagents, and a third plurality of sample wells containing immobilized nucleic acid detection reagents. The kit also comprises a holder for holding at least one of the first plurality of sample wells, at least one of the second plurality of the sample wells, and at least one of the third plurality of sample wells. Preferably, different ones of the first plurality of samples wells contain different dried nucleic acid decontamination reagents, different ones of the second plurality of

sample wells contain different dried nucleic acid amplification reagents, and different ones of the third plurality of sample wells contain different immobilized nucleic acid detection reagents. By virtue of this arrangement, the user can select the specific sample wells that are needed for a particular nucleic acid assay, assemble the selected sample wells in the required order using the holder, and place the holder into an automated processing apparatus to carry out the desired assay. In a preferred embodiment; each sample well in the first, second and third plurality of sample wells comprises one of a series of connected sample wells which are substantially identical to each other, and the holder is adapted to hold all of the connected sample wells in each of the first, second and third plurality of sample wells. In this way, a number of nucleic acid assays can be carried out simultaneously on different liquid biological samples.

Brief Description of the Drawings

The various objects, advantages and novel features of the present invention will be more readily understood from the following detailed description when read in conjunction with the appended drawings, in which:

Fig. 1 is a perspective view of an array of covered sample wells constructed in accordance with a preferred embodiment of the present invention, with the sample wells being connected to each other in strips and carried in a holder suitable for use in an automated processing apparatus;

Fig. 2 is a perspective view similar to that of Fig. 1, with one strip of connected sample wells shown removed from the holder and the caps shown removed from the strip sample wells;

Fig. 3 is a perspective view similar to that of Figs. 1 and 2, with all of the sample wells removed in order to show the configuration of the empty holder;

Fig. 4 is a sectional view taken along the line 4-4 in Fig. 2, illustrating the internal details of the sample wells and certain features of an automated processing apparatus with which the sample wells and holder may be used;

Fig. 5 is a top plan view of a portion of an automated processing apparatus in which the sample wells may be placed, showing the configuration of the heating platens which are used to heat the liquid samples within the sample wells;

Figs. 6-11 are sequence views illustrating the manner in which a nucleic acid assay may be carried out using the sample wells of the present invention;

Figs. 12 and 13 illustrate modified sample wells in accordance with the present invention, utilizing different types of cap structures;

Figs. 14 and 15 illustrate modified sample wells in accordance with the present invention, utilizing different bottom configurations; and

Fig. 16 illustrates the manner in which the sample wells of the present invention may be provided in the form of a kit which allows the user to select the specific process steps to be carried out on a liquid sample in an automated processing apparatus.

Throughout the drawings, like reference numerals will be understood to refer to like parts and components.

Detailed Description of the Preferred Embodiments

A multiple sample well assembly 20 constructed in accordance with a preferred embodiment of the present invention is illustrated in Figs. 1-3. The assembly comprises a holder or tray 22, which is generally rectangular in shape, and a plurality of strips 24 of connected sample wells 26. In the preferred embodiment, each strip 24 includes twelve sample wells 26, divided into four groups 28 of three sample wells 26 each. Other configurations of strips and groups of sample wells are, of course, possible. The groups 28 are connected to each other by means of breakable tabs 30 which are provided on alternating sides of the strip 24 of sample wells, as shown. By breaking one or more of the tabs 30, the user can reduce the number of sample wells 26 in each strip 24 (by multiples of 3) to suit the requirements of the assay being performed. Within each group 28, the sample wells 26 are connected to each other by means of an upper horizontal flange 32 and vertical webs (not visible in Figs. 1-3) which are formed between adjacent wells immediately below the flange 32. The sample wells 26 are cylindrical in shape with open tops and flat bottom surfaces. Each strip 24 of sample wells 26 is preferably formed integrally from a suitable plastic material, such as polystyrene, although other materials may be used if desired. As described thus far, the construction of the strip 24 of sample wells 26 is essentially identical to that described in the aforementioned co-pending patent application Serial No. 08/409,821, in which the wells are used in the detection step of an automated nucleic acid assay.

The holder 22 is provided with a rectangular grid or lattice 34 for receiving a plurality of strips 24 of connected sample wells 26. Each rectangular opening 36 in the grid 34 is dimensioned to frictionally receive and hold the cylindrical base portions 38 of two adjacent sample wells 26 from

adjoining strips 24. The rectangular grid openings are bisected by downwardly recessed walls 39 which extend in the lengthwise direction of the holder 22. The walls 39 are provided with alternating 45° gaps 40, as shown in Fig. 3, to provide the walls with some degree of resiliency. By virtue of these gaps 40, each wall 39 is divided into two sections which can flex independently of each other and in opposite directions. This allows the walls 39 to exert an independent gripping force on each strip 24 of sample wells 26 independently, regardless of the presence or absence of an adjoining strip 24 of sample wells 26 in the holder 22. In the preferred embodiment, the holder 22 accommodates eight strips 24 of sample wells 26 and therefore carries a total of 96 individual sample wells 26 when the holder 22 is completely filled. The 96-well format is preferred since it is similar to that of a standard 96-well microtiter plate, although other configurations can be used if desired. The holder 22 is preferably molded or machined in one piece from a suitable plastic material, such a polystyrene, although other materials can be used to suit the requirements of particular applications. Specically, if the process conducted in the sample well requires heat, the holder 22 may be contructed of heat resistant plastic or other material such as G.E. ULTEM® (polyethyleneimide) or DELRIN® available from DuPont. Alternatively, the heating platens which provide heat through the holder to the sample wells may be designed in a manner to limit the area of the holder which is heated, thus permitting the use suitable plastc materials other than heat resistant plastics.

Merely by way of example, but not by way of limitation, the holder 22 may be approximately 5.0 inches in length, approximately 3.3 inches in width, and approximately 0.5 inches in height. The grid openings 36 are rectangular with dimensions of approximately 0.3 inch by 0.7 inch, and are bisected by the recessed walls 39 to create square openings having a dimension of about 0.3 inch on each side. Each strip 24 of sample wells 26 is approximately 0.36 inch in width (measured to the outer edges of the flange 32) and approximately 0.5 inch in height. Each sample well 26 has a generally cylindrical shape with a slight inward taper of about 2° from top to bottom. The diameter of the top opening 42 of the sample well 26 is approximately 0.26 inch, and the interior volume of the sample well 26 is approximately 4.25 microliters (μL).

In accordance with an important aspect of the present invention, means are provided for covering or capping the sample wells 26 to reduce evaporative sample loss and cross-contamination between samples when the sample wells 26 are used in a nucleic acid assay, immunoassay or other biological or chemical process. In the preferred embodiment, this is achieved by means of a strip 44 of flexible plastic or rubber caps 46, with one cap 46 being provided for each of the sample wells 26. The center-to-center spacing between adjacent caps 46 corresponds to the center-to-center spacing

between the respective top openings 42 of the sample wells 26. Each cap 46 has a cylindrical or disk-like shape and is connected to the next cap by means of a breakable tab 48, so that the strip 44 of caps 46 can be broken or subdivided by the user in the same manner as the strip 24 of sample wells 26. On the underside of each cap 46, an integral resilient cylindrical stopper portion 52 is formed. The stopper portion 52 is dimensioned so that it fits tightly within the top opening 42 of the corresponding sample well 26 when the cap 46 is installed on the sample well 26. During normal use of the sample well assembly 20, all of the sample wells 26 in the holder 22 will have caps 46 fitted in their top openings as illustrated in Fig. 1.

As will be evident from Figs. 1 and 2, each cap 46 is provided with a pre-formed circular hole or aperture 54 having a vertical axis and located at or near the center of the cap. When the cap 46 is installed on the corresponding sample well 26, the aperture 54 communicates with the interior portion of the sample well 26 and provides an access opening through which sample liquids can be introduced into (and withdrawn from) the sample well 26 by means of a manual or robotic pipetting apparatus, as will be described in detail shortly. In the preferred embodiment, the diameter of the aperture 54 is approximately 0.09 inch, corresponding to the diameter of a standard disposable pipette tip (which is conical in configuration) at a point approximately 0.47 inch above the distal end of the tip.

Fig. 4 is a sectional view taken along the line 4-4 in Fig. 1, illustrating the manner in which the sample wells 26 may be used to carry out a nucleic acid assay. Eight sample wells 26A-26H are shown in Fig. 4, with each sample well being part of a different strip 24 of sample wells in Figs. 1 and 2. In a typical application, each strip 24 of sample wells 26 in Figs. 1 and 2 will be adapted to carry out a different step of the nucleic acid assay, and a manual or robotic pipetting apparatus is used to transfer the liquid sample from each well of a given strip to the corresponding well of the next strip. Thus, with the 96-well arrangement shown in Figs. 1 and 2, simultaneous nucleic acid assays can be carried out on as many as twelve samples (one for each well position in a given strip 24), and for each sample the steps of the assay can be carried out in as many as eight different sample wells (corresponding to the number of strips 24 of sample wells 26 that are accommodated by the holder 22). Fig. 4 also illustrates various heating platens and optical detectors that may be used in an automated processing apparatus when a nucleic acid assay is being carried out, and the operation of these elements will become apparent in the description which follows.

With continued reference to Fig. 4, the first sample well 26A may be used as a "heat spike" well in a nucleic acid assay. For this reason, the automatic processing apparatus into which the

holder 22 is placed is provided with a heating platen 56 which is situated below the sample well 26A. The heating platen 56 is operated to raise the temperature of the liquid sample in the sample well 26A to approximately 80°C during the initial heat spike step. Since some types of plastic materials (such as polystyrene) can soften or melt at this temperature, the sample well 26A can be made of a ceramic material or other heat-resistant material if desired. This would also be true for all of the other sample wells in the strip 24 of which the well 26A of Fig. 4 is a part.

The second sample well 26B in Fig. 4 will typically serve as a decontamination well when a nucleic acid assay is being carried out. The purpose of the decontamination step is to deactivate contaminating amplicons in the liquid sample before the amplification step is carried out, so that only the desired target nucleic acid sequence is amplified. The decontamination reagents that are required for the decontamination reaction are preferably provided in the form of a dried spot 58 which is adhered to the bottom of the sample well 26B. Conventional equipment for spotting microtiter wells may be used to form the spots 58 in a plurality of sample well strips 24 (including an entire holder of sample well strips) during the manufacturing process, and the spots may be dried in a convection drying oven under conditions of controlled temperature and humidity or lyophilized. However, the preferred method for drying some decontamination reagents 58 is to dry the reagents in the presence of trehalose as taught in U.S. Patent No. 4,891,319 and Patent Cooperation Treaty International Publication No. WO 87/00196, both owned by Quadrant Bioresources, Ltd. and incorporated herein by reference. Briefly, the preferred drying technique protects biological materials against denaturation during drying and involves subjecting an aqueous system containing the biological material to a temperature above freezing in the presence of trehalose in an amount between 0.05 and 20 weight percent based on the total weight of the aqueous system. Trehalose is a naturally occurring, non-reducing disaccharide also known as α-D-glucopyranosyl-α-D-glucopyranoside. The drying in the presence of trehalose may be simple air drying, preferably at atmospheric pressure. In the drying of the decontamination reagents 58, trehalose technology is an excellent system for drying in a reagents to be used in the present invention. The decontamination reagents may be provided in any suitable form, including (but not limited to) a solid such as a dried film, lyophilized pellets, or proper impregnated with the reagents.

Since the decontamination step is generally carried out at a temperature of about 41°C or higher, a heating platen 62 is provided in the automated processing apparatus and is situated below the decontamination well 26B. The heating platen 62 is preferably separate from the heating platen 56, since the latter heating platen operates at a higher temperature. By separating the heating platens

56 and 62, the decontamination well 26B can be isolated from the higher temperature that is applied to the heat spike well 26A, and hence the well 26B need not be made of a heat-resistant material.

The third sample well 26C in Fig. 4 will typically serve as an amplification well during a nucleic acid assay. For this purpose, a dried spot 60 containing suitable nucleic acid amplification reagents is adhered to the bottom of the sample well 26C, as shown. The trehalose technology used for drying the decontamination reagents 58 is also preferred for drying of the amplification reagents 60. As in the case of the decontamination reagents, the amplification reagents 60 may be provided in any suitable form, including (but not limited to) a solid such as a dried film, lyophilized pellets, or paper impregnated with the reagents. In the preferred embodiment of the present invention, the amplification method used is Strand Displacement Amplification including thermophilic Strand Displacement Amplification. However, other possible amplification techniques include Polymerase Chain Reaction (PCR), Ligase Chain Reaction (LCR), transcription-based amplification, self-sustained sequence replication (3SR), the Qβ replicase system, nucleic acid sequence-based amplification (NASBA), the repair chain reaction (RCR), and boomerang DNA amplification (BDA).

For example, during the amplification step of SDA, the liquid sample is incubated for approximately two hours at a temperature of about 41°C. In order to heat the liquid sample to the desired temperature, a heating platen 64 is provided in the automated processing apparatus and is situated below the amplification well 26C, as shown. At the end of the incubation period, the amplification reaction is stopped by operating the heating platen 64 to raise the temperature of the sample to about 80°C for approximately five minutes. The amplification well 26C may be made of a ceramic material or other heat-resistant material in order to withstand this temperature. As before, the heating platen 64 is preferably made physically separate from the adjacent heating platens so that the sample wells associated with the adjacent platens are not required to withstand high temperatures.

With continued reference to Fig. 4, the next three sample wells 26D, 26E, and 26F will typically be used for carrying out DNA target sequence detection steps at the conclusion of a nucleic acid assay. The number of detection wells used will depend upon the specific type of assay being carried out and the detection method used. In the present example, it is assumed that the purpose of the assay is to detect tubercle bacillus DNA sequences in the amplified sample. In that case, three separate detection reactions are preferably carried out in the respective sample wells 26D, 26E and 26F. The first detection reaction, carried out in sample well 26D, is an internal amplification control reaction which determines whether any nucleic acid amplification has occurred in the liquid sample.

The second detection reaction, carried out in sample well 26E, is a "genus" reaction which detects whether a mycobacterial DNA sequence has been amplified. The third detection reaction, carried out in sample well 26F, is a "species" reaction that detects any tubercle bacillus DNA sequences in the amplified sample. Typically, the amplified sample is removed from the amplification well 26C and is then divided into three equal parts (aliquots) by a robotic pipetting apparatus, with each aliquot being dispensed into one of the detection wells 26D, 26E and 26F. In order to provide a sufficient volume of liquid in each of the sample wells 26D, 26E and 26F, the amplified sample that is removed from the amplification well 26C may be mixed with an inert liquid (such as a saline solution) after it has been divided among the detection wells 26D, 26E and 26F.

The detection wells 26D, 26E, and 26F may be either generic to several different types of target DNA sequences, or specific to one particular type of DNA sequence. To create generic wells, the interior walls of the detection wells 26D, 26E and 26F are coated during manufacture with a dried capture reagent (typically biotinilated BSA/Streptavidin), and specific capture probes and detection probes are later introduced to the sample wells in liquid form during the assay using a manual or robotic pipetting apparatus. If target-specific wells are desired, the capture probes and detection probes are included in the coating that is provided on the interior walls of the sample wells during the manufacturing process.

During the detection step of a nucleic acid assay, the liquid samples in the sample wells 26D, 26E and 26F are incubated for a period of approximately one hour at a temperature of about 33°C after the capture probes and detection probes are added. In order to heat the liquid samples to the desired temperature, a heating platen 66 is provided in the automated processing apparatus and is located below the sample wells 26D, 26E and 26F. The use of a shared heating platen 66 is possible since the sample wells 26D, 26E and 26F are heated to the same temperature; however, if this is not true for a given assay, separate heating platens may be used. The final step in the detection process is typically the addition of a liquid chemiluminescent reagent to the detection wells 26D, 26E and 26F. This also involves an incubation step (approximately 30 minutes at 37°C) and produces luminescence within the microwells 26D, 26E and 26F when the chemiluminescent reagent reacts with the hybridized amplified material which has become bound to the interior walls of the detection wells. Such luminescence, which indicates that a target nucleic acid sequence has been detected, may be sensed by removing the holder 22 from the automated processing apparatus and placing it into a conventional luminometer. Alternatively, the detection of luminescence in the detection wells 26D, 26E and 26F may be carried out within the automated processing apparatus itself, as illustrated in

Fig. 4. To achieve this, the detection wells 26D, 26D 26F are made of a transparent plastic material so that the luminescence within each well can be detected externally. (The caps 46 can be, but are not required to be, transparent). Optical fibers 68, 70 and 72 are routed through holes in the heating platen 66 so that they terminate in facing relationship to the bottoms of the sample wells 26D-26F. The opposite ends of the optical fibers 68, 70 and 72 are connected to an opto-electronic detection system 74 which detects the presence of luminescence in each of the detection wells 26D-26F and provides a suitable display or readout to the user.

The last two sample wells 26G and 26H are not used in the illustrated embodiment, but are provided in order to accommodate other types of nucleic acid assays or immunoassays which may require additional liquid transfer steps and/or additional reagents. Heating platens 76 and 78 may be provided for the additional sample wells 26G and 26H if the reactions carried out in these sample wells require that the liquid sample be maintained at elevated temperatures. Otherwise, the heating platens 76 and 78 can be deleted.

Fig. 5 is an overhead view which illustrates the preferred arrangement of heating platens below the holder 22 in Fig. 4. In this preferred arrangement, each of the heating platens 56, 62, 64, 66, 76 and 78 has a generally rectangular configuration, with a height approximately equal to the length of one strip 24 of sample wells 26, and a width approximately equal to the diameter of the base portions 38 of the sample wells 26 (or, in the case of the heating platen 66, a width sufficient to extend across the base portions 38 of successive strips 24 of sample wells 26). Other alternative heating platen configurations are possible including individual circular heating platents for each sample well or movable heating platens capable of being heated to different temperatures and can be positioned under different strips of sample wells. The optical fibers 68, 70 and 72 pass through apertures in the heating platen 66, with these apertures having a center-to-center spacing equal to the center-to-center spacing between the sample wells 26 of a given strip 24. In order to detect luminescence within all twelve sample wells 26 in each of the detection well strips 24, the platen 66 includes twelve optical fibers 68, twelve optical fibers 70, and twelve optical fibers 72.

Figs. 6-11 are sequence views illustrating the manner in which a nucleic acid assay may be carried out using the improved sample well construction of the present invention. In these figures, it is assumed that the holder 22 and sample wells 26 are installed in an automated processing apparatus of the type described previously in connection with Fig. 4. In addition to the previously-described heating platens and optical detection system, the automated processing apparatus will typically include a robotic pipetting system which is capable of dispensing and transferring liquids in a

programmed manner. A suitable robotic pipetting system is the TECAN Model RSP 9682 automatic pipetting instrument manufactured by TECAN AG of Hombrechtikon, Switzerland. The robotic arm of the pipetting system includes an ejector assembly which carries a disposable plastic pipette tip 80. The disposable pipette tip 80 (the central portion of which is broken away in Figs. 6-11) has a generally conical configuration, tapering from an outer diameter of approximately 0.28 inch at its proximal end 82 to about 0.03 inch at its distal end 84. The pipette tip 80 is preferably made of autoclavable polypropylene with a maximum volume of 300 microliters (μL), and is fitted with an internal plug or insert 86 of filter material near its proximal end 82. The filter material allows air to pass so that liquids can be drawn into (and dispensed from) the opening at the distal end 84 of the pipette tip 80, but blocks the passage of liquids. The filter material is described in detail in a co-pending patent application of Michael L. Lamos et al, Serial No. 08/410,245, filed on March 24, 1995, and entitled "Pipette Tip".

In Fig. 6, a liquid biological sample 88 to be assayed has been transferred from a sample container (not shown) to the heat spike well 26A. In making this transfer, the robotic pipetting apparatus maneuvers the distal end 84 of the pipette tip 80 through the aperture 54 in the cap 46 of the heat spike well 26A, and continues to lower the pipette tip 80 into the well 26A until the distal end 84 is just above the bottom interior surface of the well. The diameter of the aperture 54 is chosen so that, when the pipette tip 80 reaches this position, the aperture 54 is substantially closed or occluded by the pipette tip 80. In effect, therefore, the pipette tip 80 (together with the cap 46) serves as a closure or seal for the well 26A after the liquid sample 88 has been introduced. The pipette tip 80 is allowed to remain in the position shown in Fig. 6 throughout the heat spike interval (during which the heating platen 56 is operated to raise the temperature of the liquid sample 88 to approximately 80°C), thereby reducing or eliminating evaporative loss of the sample during this interval. Any liquid aerosol which may be formed in the well 26A is also prevented from leaving the well by the pipette tip 80, thereby avoiding cross-contamination with other liquid samples being processed by the automated processing apparatus. When the heat spike interval expires, the liquid sample is drawn back into the pipette tip 80 by the robotic pipetting apparatus, so that it can be transferred to the next sample well 26B for decontamination. A new pipette tip may be used for this transfer of sample.

In Fig. 7, the liquid biological sample 88 has been transferred into the decontamination well 26B by the automated pipetting apparatus. As described previously in connection with Fig. 6, the distal end 84 of the pipette tip 80 has passed through the aperture 54 in the cap 46 of the well 26B,

and has been brought almost into contact with the bottom interior surface of the well 26B. In this condition, the pipette tip 80 effectively closes off the decontamination well 26B from the ambient atmosphere. When the liquid sample 88 is introduced into the decontamination well 26B by the pipette tip 80, it mixes with and rehydrates the dried decontamination reagents in the spot 58. The heating platen 62 is operated to raise the temperature of the liquid sample 88 to approximately 41°C, and this temperature is maintained for an incubation period of approximately 50 minutes. Throughout this interval, the disposable pipette tip 80 is maintained in the position shown in Fig. 7 to minimize evaporative loss of the sample 88 and to prevent the escape of aerosols from the decontamination well 26B. When the decontamination reaction is complete, the heating platen 64 is deactivated and the liquid sample 88 is drawn back into the pipette tip 80.

In Fig. 8, the liquid sample has been transferred from the decontamination well 26B to the amplification well 26C by the pipette tip 80. When the liquid sample 88 is introduced into the amplification well 26C, it mixes with and rehydrates the dried amplification reagents in the spot 60. The heating platen 64 is operated to raise the temperature of the liquid sample to about 42°C, and this temperature is maintained for an incubation period of approximately two hours. Throughout this interval, the pipette tip 80 is allowed to remain in the position shown in Fig. 8 to reduce evaporative loss of the liquid sample and prevent cross-contamination with other samples. The amplification reaction is stopped by operating the heating platen 64 to raise the temperature of the liquid sample to 80°C for approximately five minutes. After the five-minute heat spike (during which the pipette tip 80 remains in the position shown), the heating platen 64 is deactivated and the liquid sample 88 is drawn back into the pipette tip 80. If desired, the heat spike step that terminates the amplification reaction can be carried out in a separate sample well which has better heat resistance characteristics, rather than in the amplification well 26C.

The detection portion of the nucleic acid assay, which involves the detection wells 26D, 26E and 26F, is shown in Figs. 9-11. In Fig. 9, all or a portion of the liquid sample 88 (to which, in the latter case, a saline solution or other inert liquid may be added to maintain an adequate sample volume) has been introduced into the first detection well 26D, whose internal walls are coated with dried capture reagent(s). (If desired, portions or aliquots of the sample 88 may be introduced into the sample wells 26E and 26F at this time, as shown ("aliquot method"); alternatively, since the detection reactions are independent of each other, the entire sample 88 may be transferred from one sample well to the next during the detection procedure.) Suitable capture probes and detection probes (in liquid form) are then obtained from external reagent containers and added to the liquid

sample 88 by means of the pipette tip 80. A new pipette tip is required before each probe is added, in order to prevent contamination of the reagent containers. After the capture and detection probes have been added, the heating platen 66 is operated to raise the temperature of the liquid sample to about 33°C, and this temperature is maintained for an incubation period of about one hour. During this period, the pipette tip 80 remains in the position shown in Fig. 9 to close off the detection well 26D. After the incubation period, the heating platen 66 is deactivated and the liquid sample 88 is removed from the detection well 26D by the pipette tip 80 and is either discarded (aliquot method) or transferred to the next detection well 26E. A wash step may then be carried out (either by the pipette tip 80 or by a separate wash head) to remove any remaining sample and reagents from the detection well 26D. This leaves only the reacted material which is bound to the inside walls of the well 26D. The pipette tip 80 is then used to draw a quantity of chemiluminescent reagent from an external reagent container, and to introduce the chemiluminescent reagent into the detection well 26D. (Typically, the volume of chemiluminescent reagent is about three times the volume of the sample aliquot which was in the sample well.) The heating platen 66 is operated to incubate the chemiluminescent reagent in the detection well 26D at 37°C for approximately 30 minutes. During this interval, the chemiluminescent reagent reacts with any hybridized amplified material which may have become bound to the interior walls of the detection well 26D. The resulting luminescence, indicating that a target nucleic acid sequence has been detected, is sensed by the detection system 74 of Fig. 4 through the optical fiber 68. The pipette tip 80 may be left in the position shown in Fig. 9 during the chemiluminescent incubation period if desired, although this is not essential since evaporative loss and cross-contamination is not of great concern at this stage.

In the preferred embodiment of the invention, the detection reaction carried out in the detection well 26D is an internal amplification control reaction which indicates whether any nucleic acid amplification has occurred in the liquid sample 88. This is followed by a "genus" reaction which takes place in the detection well 26E, and by a "species" reaction that takes place in the last detection well 26F. These detection reactions are illustrated in Figs. 10 and 11, respectively. The series of operations carried out during the genus and species reactions are the same as those described previously in connection with Fig. 9, except that different capture and detection probes are used.

In the foregoing description of Figs. 6-11, it has been assumed that the detection wells 26D, 26E and 26F are of the "generic" type, requiring specific capture and detection probes to be obtained from external reagent containers. However, the capture and detection probes may be provided as part of the coating on the interior walls of the detection wells 26D, 26E and 26F, along

with the dried capture reagent(s) in order to minimize the number of liquid transfer steps which must be carried out by the robotic pipetting apparatus. In other alternative embodiments, capture and detection of multiple targets may occur simultaneously in a single well through the use of different detection systems for different targets.

In introducing the pipette tip 80 into each of the sample wells 26A through 26F, the robotic pipetting apparatus causes the distal end 84 of the disposable pipette tip 80 to stop at a predetermined point just above the bottom surface of the sample well before dispensing liquid into the well, and then to remain at that position during any subsequent incubation or reaction interval to close off the sample well. However, this is not the only possible mode of operation. It may be preferred, for example, to initially leave a somewhat larger gap between the distal end 84 of the pipette tip 80 and the bottom of the sample well while the liquid sample is being introduced into the sample well. This prevents the opening at the end of the pipette tip from being occluded by the bottom surface of the sample well, and also maintains a slight annular gap between the pipette tip and the circumferential edges of the aperture 54 to assist in venting air from the sample well while the liquid sample is being dispensed. After the dispensing operation is concluded, the distal end 84 of the pipette tip 80 may be lowered to a point closer to (or in contact with) the bottom surface of the sample well. In this position, the outer walls of the pipette tip are very close to (or in contact with) the circumferential edges of the aperture 54, thereby effectively sealing the sample well during the subsequent incubation or reaction interval. When the liquid sample is to be withdrawn from the sample well, the distal end 84 of the pipette tip 80 may be elevated slightly above the bottom surface of the sample well to allow the liquid sample to flow freely into the opening of the pipette tip and to permit venting of the sample well 26.

Fig. 12 illustrates a modified cap structure which may be used in connection with the sample wells 26. The interconnected caps 46' of Fig. 12 are similar to the caps 46 described previously in connection with Fig. 2, except that the pre-formed apertures 54 are not used. Instead, the top central portion 88 of each cap is provided in the form of a thin resilient membrane or septum made of rubber, plastic film or the like, and two or more intersecting slits 90 and 92 in a cross pattern are formed completely through the membrane. The slitted membrane serves as the equivalent of a solid cap or cover when the pipette tip 80 is not present, but is easily penetrated by the distal end 84 of the pipette tip 80 when it is desired to introduce a liquid sample into the well 26 or to withdraw a previously introduced liquid sample from the well 26. In some cases, the slitted membrane 88 may create a better seal with the outside surfaces of the pipette tip 80 than would be possible with the

pre-formed apertures 54 shown in Fig. 2.

A further modification of the cap structure used for the sample wells 26 is illustrated in Figs. 13. In this embodiment, the discrete caps 46 or 46' are replaced by a substantially flat, continuous strip 94 of thin flexible material such as acetate or rubber or styrene sheet or film which is secured by means of an adhesive to the top openings 42 of the sample wells 26. The adhesive may be provided either on the lower surface of the strip 94, or on upper surfaces of the sample wells 26. Score lines 96 and 98 may be formed partially through the upper surface of the strip 94 (preferably in a cross-pattern as shown) to assist the distal end 84 of the pipette tip 80 in penetrating the strip 94. The length of the strip 94 is such that a single strip is sufficient to cover all of the wells 26 in a given strip 24 of sample wells, although the strip 94 can be cut or subdivided if fewer than all of the wells 26 in a given strip 24 of sample wells are used.

Figs. 14 and 15 illustrate two alternative bottom configurations which may be used for the sample wells 26. In Fig. 14, the bottom 100 of the sample well 26' is spherically rounded, while in Fig. 15 the side walls 102 of the sample well 26'' are conical. These alternative configurations may be useful in providing a greater usable surface area within the sample well (particularly when reagents are adhered to the internal walls of the sample well), and in promoting better mixing between the liquid sample dispensed from the pipette tip 80 and any reagents that may be provided in the sample well.

Fig. 16 illustrates the manner in which the sample wells 26 and holder 22 may be provided to the end user in the form of a kit which allows the user to design a specific type of nucleic acid assay (chosen from among several options) to be carried out manually or in an automated processing apparatus. In the illustrated example, the kit includes three strips of decontamination wells 24-1, 24-2 and 24-3 of different types. As an example, the strip 24-1 of decontamination wells may contain reagents for a standard uracil DNA glycosylase (UDG) decontamination reaction, the strip of 24-2 of decontamination wells may contain reagents for a temperature-resistant decontamination reaction, and the strip 24-3 of decontamination wells may contain reagents for a chemical decontamination reaction. One of these strips is chosen by the manufacturer or user for the specific assay that is to be performed, and is placed in the holder 22 at the position reserved for the strip of decontamination wells. Similarly, two strips of amplification wells 24-4 and 24-5 are provided in the kit. The wells of the first strip 24-4 may be provided with reagents suitable for the amplification of target DNA sequences from the tubercle bacillus, and the second strip 24-5 may be provided with reagents suitable for the detection of target DNA sequences from another type of bacterium, such as the

chlamydia bacterium. Depending upon the specific pathogen for which the assay is being conducted, one of the strips 24-4 or 24-5 will be selected by the user and placed in the position reserved for the amplification strip in the holder 22. Finally, the kit includes six strips 24-6 through 24-11 make up detection wells. One or more of these strips are chosen by the user and placed in the holder 22 at the positions reserved for the detection well strips. In the illustrated example, the detection wells strips 24-6, 24-7 and 24-8 may contain signature, genus and species detection reagents, respectively, for target DNA sequences from the tubercle bacillus. The remaining strips 24-9, 24-10 and 24-11 of detection wells may contain similar reagents for detecting chlamydia, gonorrhea, or other pathogens.

In general, the liquid sample employed in the present invention will be an aqueous preparation containing the target nucleic acid (i.e., ribonucleic acid (RNA) or deoxyribonucleic acid (DNA)) and any contaminating amplicons, with either (or both) the target nucleic acid and the amplicons in single-stranded form. For example, the target nucleic acid may comprise randomly sheared genomic DNA fragments. The preparation will be in a form suitable for use in a nucleic acid amplification procedure, in accordance with known techniques.

Decontamination to remove contaminating amplicons in a sample containing target nucleic acid sequence may be carried out by any suitable means, including the techniques taught in U.S. Patent No. 5,035,996 or published European Patent Application No. 0 415 755 A2, both of which are incorporated herein by reference. These patent publications are owned by Life Technologies Inc. and describe a decontamination technique wherein deoxyuridine (dUTP) is used in the amplification procedure. Then, after amplification, any amplicons which may contaminate another sample are subjected to an enzymatic treatment with uracil DNA glycosylase (UDG) to render the amplicons containing dUTP substantially unamplifiable.

Amplification of a selected, or target, nucleic acid sequence may be carried out by any suitable means. *See generally* D. Kwoh and T. Kwoh, *Am. Biotechnol. Lab.* 8, 14 - 25 (1990). Examples of suitable amplification techniques include, but are not limited to, Polymerase Chain Reaction (PCR), ligase chain reaction (LCR), Strand Displacement Amplification (SDA) including tSDA, transcription-based amplification (see D. Kwoh et al, *Proc. Natl. Acad Sci. USA* 86, 1173 - 1177 (1989)), self-sustained sequence replication (or "3SR") (see J. Guatelli et al, *Proc. Natl. Acad Sci. USA* 87, 1874 - 1878 (1990)), the Qβ replicase system (see P. Lizardi et al, *Bio Technology* 6, 1197 - 1202 (1988)), nucleic acid sequence-based amplification (or "NASBA") (see R. Lewis, *Genetic Engineering News* 12 (9), 1 (1992)), the repair chain reaction (or "RCR") (see R. Lewis, *supra*), and boomerang DNA amplification (or "BDA") (see R. Lewis *supra*). Strand Displacement

Amplification (or "SDA") including thermophilic Strand Displacement Amplification ("tSDA"), is preferred.

Strand Displacement Amplification or tSDA may be carried out in accordance with known techniques. *See generally* G. Walker et al, *Proc. Natl. Acad. Sci. USA* 89, 392 - 396 (1992); G. Walker et al, *Nucleic Acids Res.* 20, 1691 - 1696 (1992), U.S. Patent No. 5,455,166, U.S. Patent No. 5,270,184 and U.S. Patent No. 5,422,252, all of which are incorporated herein by reference.

The foregoing is illustrative of the present invention, and is not to be construed as limiting thereof, as numerous alternatives to the devices and methods described which incorporate the present invention will be apparent to those skilled in the art. For example, it is within the scope of the invention to form the caps 46 integrally with the sample wells 26, or to close off the apertures 54 in the caps 46 with devices or structures other than disposable pipette tips. It is also within the scope of the invention to draw all or part of the liquid sample 88 back into the pipette tip while a reaction is occurring within one of the sample wells 26, in order to further reduce evaporative losses and cross-contamination. Finally, although the invention has been described primarily with reference to nucleic acid assays, it is also applicable to immunoassays and to other biological and chemical processes that are carried out on liquid samples. The invention is accordingly defined by the following claims, with equivalents of the claims to be included therein.

What is Claimed is:

1. An apparatus for carrying out a biological or chemical process on a liquid sample, comprising:

a sample well for receiving said liquid sample, said sample well having an interior portion and a top opening communicating with said interior portion;

a cap receivable in said top opening, said cap having a restricted aperture smaller than said top opening for communicating with the interior portion of said sample well; and

a reagent affixed within the interior portion of said sample well for reacting with said liquid sample.

2. An apparatus as claimed in claim 1, wherein said restricted aperture is substantially circular and has a diameter sufficient to receive at least the distal portion of a conical disposable pipette tip.

3. An apparatus as claimed in claim 2, wherein the diameter of said aperture is substantially equal to the diameter of said conical disposable pipette tip at a point along the length of said pipette tip.

4. An apparatus as claimed in claim 3, wherein the distance between said point and the distal end of said pipette tip is substantially equal to the distance between said restricted aperture and the bottom of said sample well when said cap is received in said top opening.

5. An apparatus as claimed in claim 1, wherein said reagent comprises a dried nucleic acid decontamination reagent adhered to an interior wall of said sample well.

6. An apparatus as claimed in claim 1, wherein said reagent comprises a dried nucleic acid amplification reagent adhered to an interior wall of said sample well.

7. An apparatus as claimed in claim 1, wherein said reagent comprises an immobilized nucleic acid detection reagent adhered to an interior wall of said sample well.

8. An apparatus as claimed in claim 1, wherein said sample well comprises one of a plurality of connected sample wells which are substantially identical to each other.

9. An apparatus as claimed in claim 8, wherein said cap comprises one of a plurality of connected caps which are substantially identical to each other.

10. An apparatus as claimed in claim 9, wherein said caps include stopper portions for engaging the top openings of said sample wells.

11. An apparatus as claimed in claim 9, wherein said caps are provided in the form of a substantially flat, continuous strip which is attachable to said plurality of sample wells by means of an adhesive.

12. An apparatus as claimed in claim 9, wherein said plurality of sample wells are connected to each other in a first substantially linear strip, and said plurality of caps are connected to each other in a second substantially linear strip.

13. An apparatus as claimed in claim 1, wherein said sample well includes a substantially transparent portion.

14. An apparatus as claimed in claim 1, wherein said sample well is made of a ceramic material.

15. A method for carrying out a biological or chemical process on a liquid sample, comprising the steps of:

drawing said liquid sample into a pipette tip;

introducing a distal portion of said pipette tip into a sample well through a restricted aperture in said sample well;

transferring said liquid sample from said pipette tip into said sample well; and

carrying out a reaction on said liquid sample in said sample well while maintaining the distal portion of said pipette tip in said restricted aperture.

16. The method of claim 15, wherein the outer surfaces of said pipette tip are brought into sufficiently close proximity with the edges of said aperture so that said pipette tip forms a closure for said aperture during said reaction.

17. The method of claim 16, wherein the distal end of said pipette tip is brought into close proximity with the bottom of said sample well, and wherein said method further comprises the step of drawing said liquid sample back into said pipette tip after said reaction is complete.

18. The method of claim 15, wherein the step of carrying out a reaction on said liquid sample in said sample well includes bringing said liquid sample into contact with a reagent contained within the interior portion of said sample well.

19. The method of claim 15, wherein said reagent comprises a dried nucleic acid decontamination reagent.

20. The method of claim 15, wherein said reagent comprises a dried nucleic acid amplification reagent.

21. The method of claim 15, wherein said reagent comprises an immobilized nucleic acid detection reagent.

22. The method of claim 15, wherein the step of carrying out a reaction on said liquid sample in said sample well includes heating said liquid sample.

23. The method of claim 15, wherein said restricted aperture is pre-formed in said sample well.

24. The method of claim 15, wherein said restricted aperture is formed during said step of introducing a distal portion of said pipette tip into said sample well by causing said pipette tip to penetrate a penetrable portion of said sample well.

25. A kit for carrying out a nucleic acid assay on a liquid biological sample, comprising:
a first plurality of sample wells containing dried nucleic acid decontamination reagents;
a second plurality of sample wells containing dried nucleic acid amplification reagents;
a third plurality of sample wells containing immobilized nucleic acid detection reagents; and
a holder for holding at least one of said first plurality of sample wells, at least one of said

second plurality of sample wells, and at least one of said third plurality of sample wells.

26. A kit as claimed in claim 25, wherein different ones of said first plurality of sample wells contain different dried nucleic acid decontamination reagents.

27. A kit as claimed in claim 25, wherein different ones of said second plurality of sample wells contain different dried nucleic acid amplification reagents.

28. A kit as claimed in claim 25, wherein different ones of said third plurality of sample wells contain different immobilized nucleic acid detection reagents.

29. A kit as claimed in claim 25, wherein each sample well in said first, second and third plurality of sample wells comprises one of a series of connected sample wells which are substantially identical to each other, and wherein said holder is adapted to hold all of the connected sample wells in each of said first, second and third plurality of sample wells.

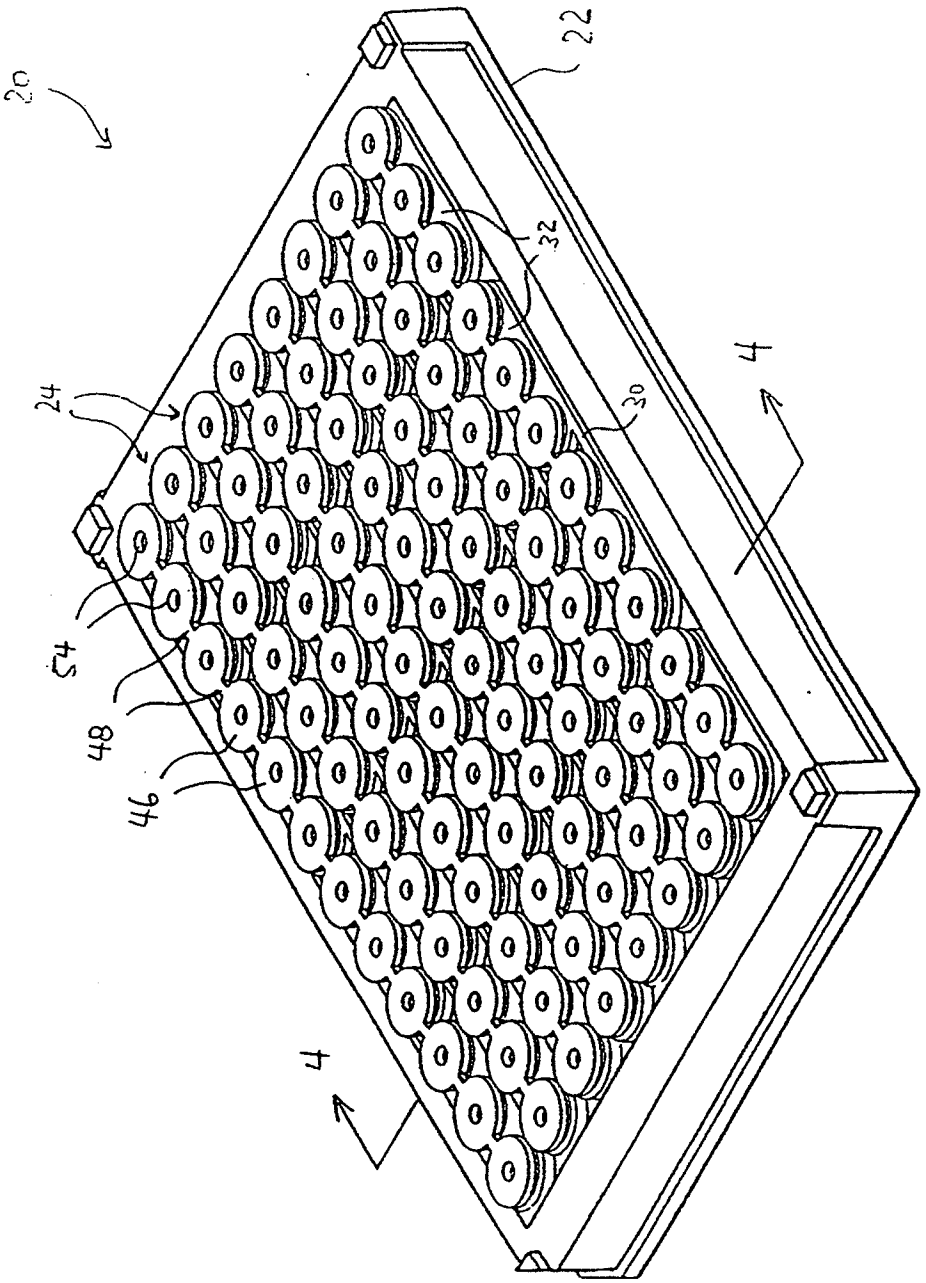
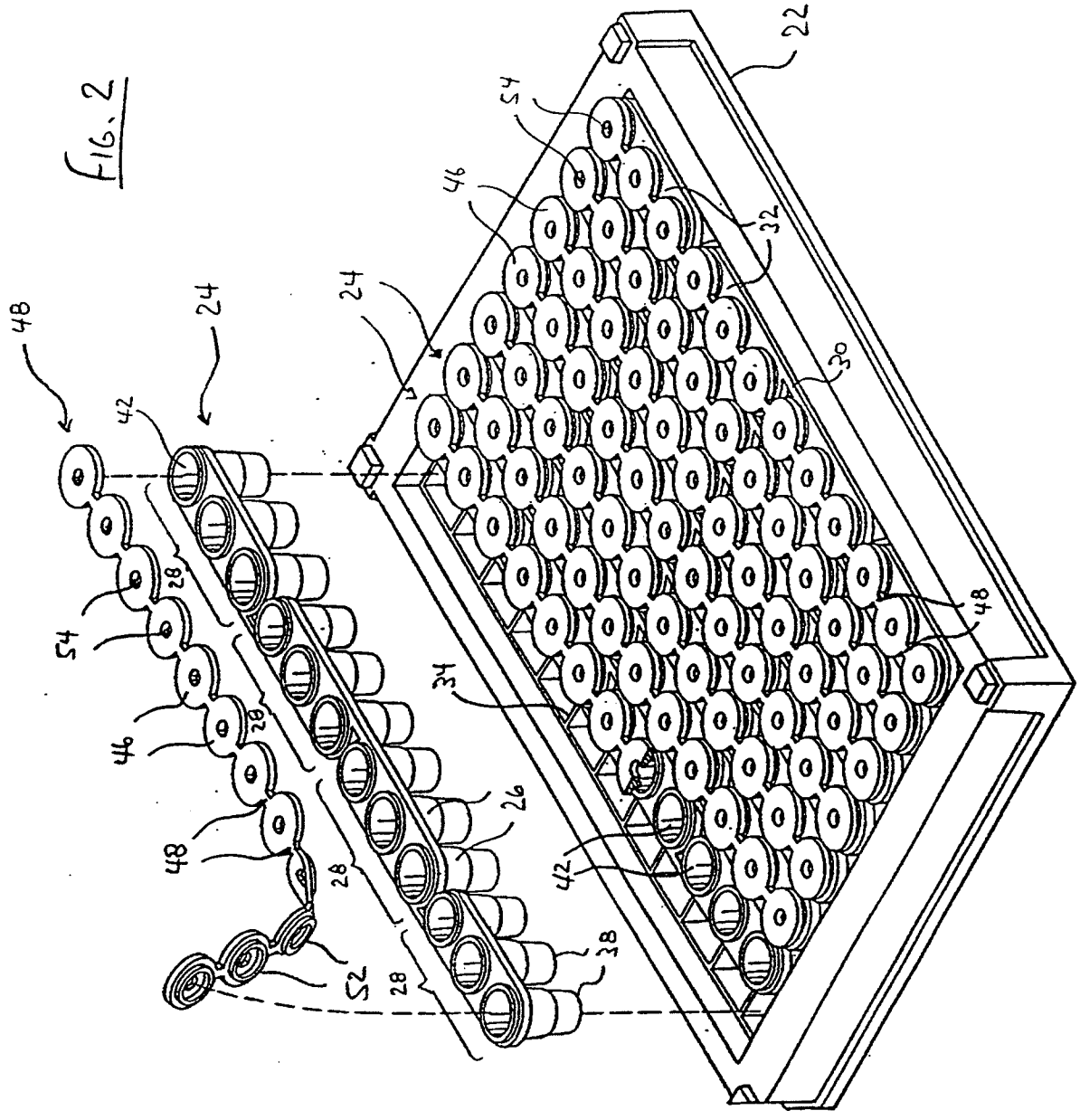


FIG. 1

FIG. 2



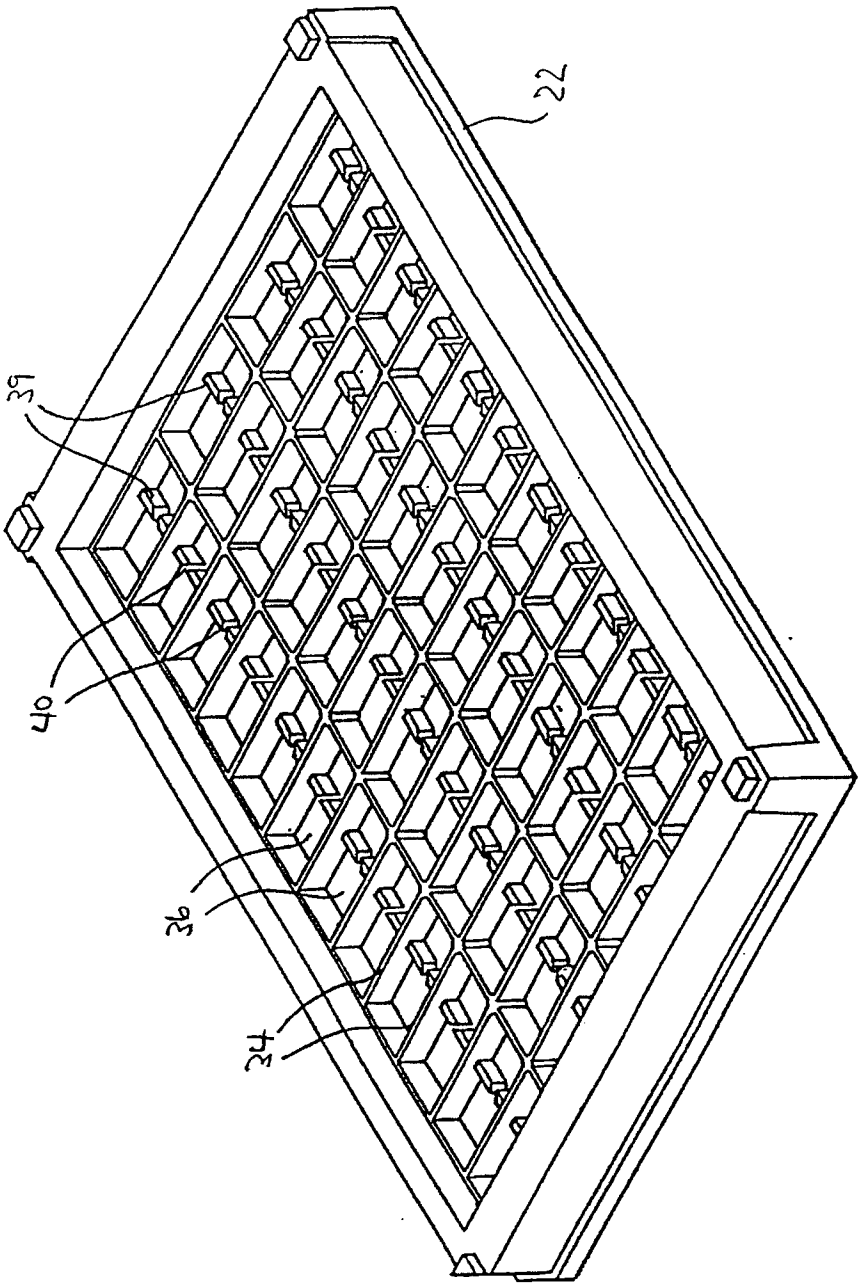
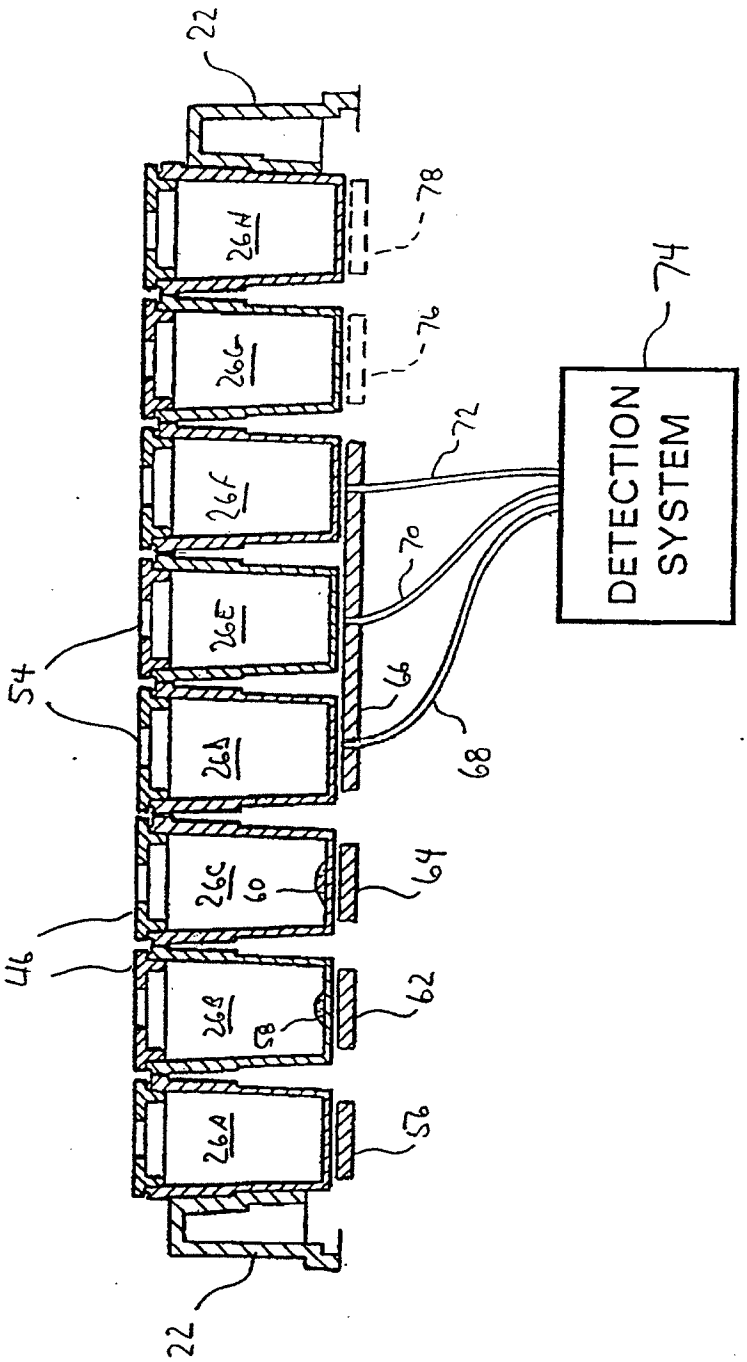


FIG. 3

FIG. 4


22
26N
78
26G
76
26F
72
74
DETECTION SYSTEM
70
26E
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66
26B
68
26C
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64
46
26A
58
62
26D
56
22

FIG. 5

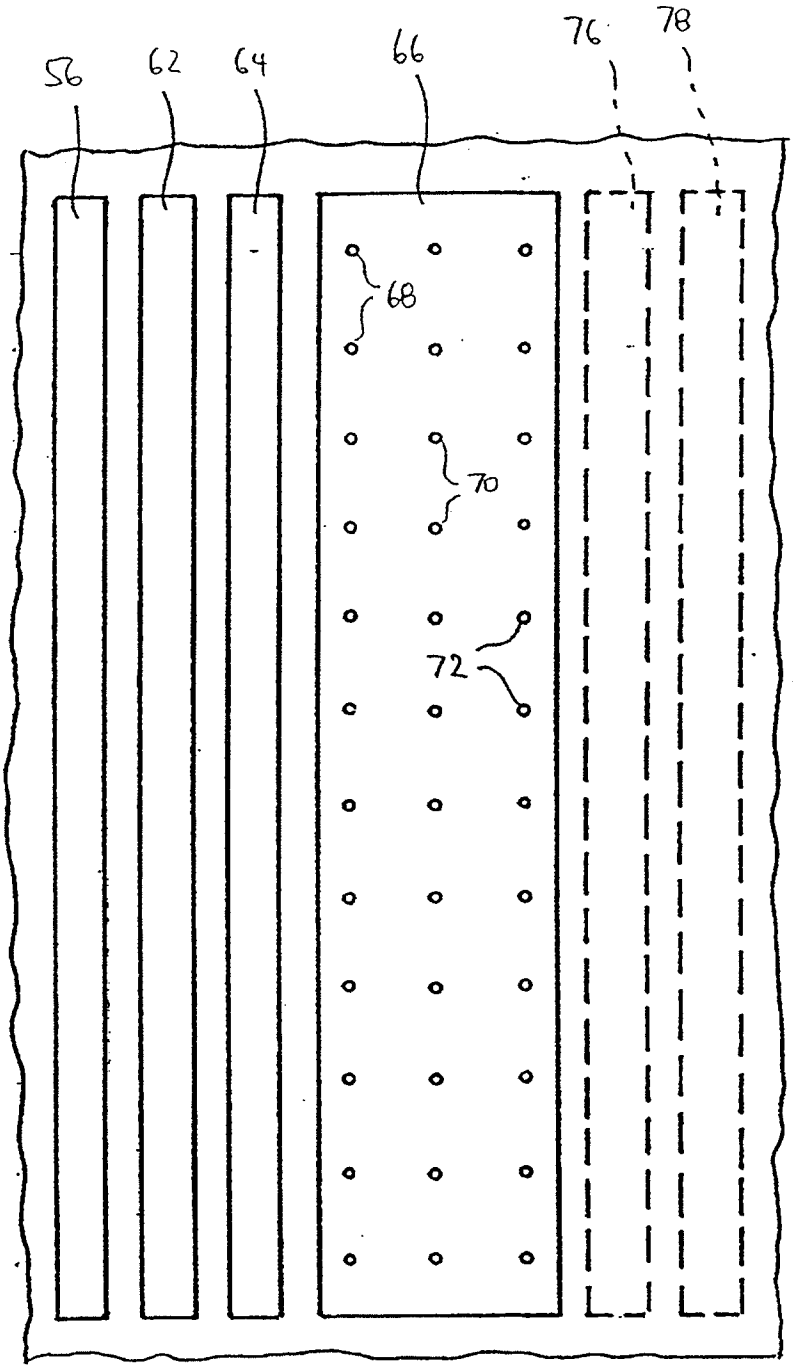

FIG. 6

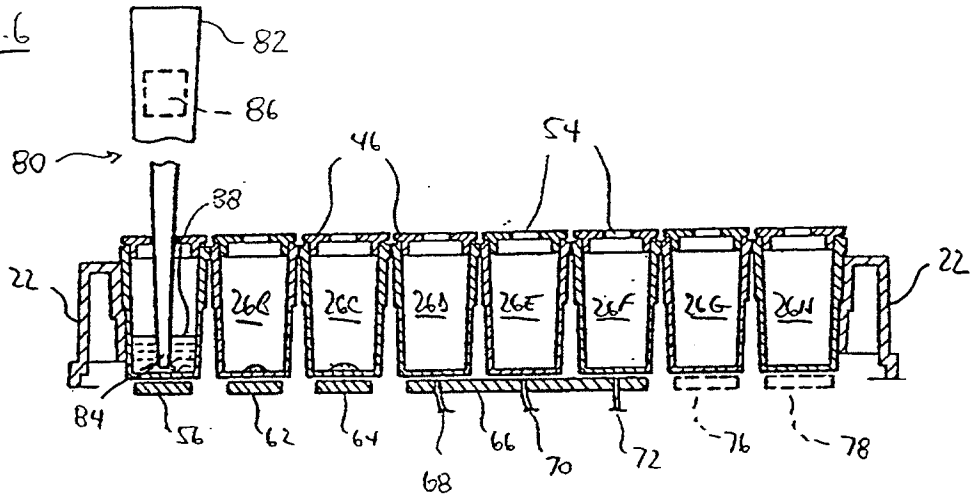

FIG. 7

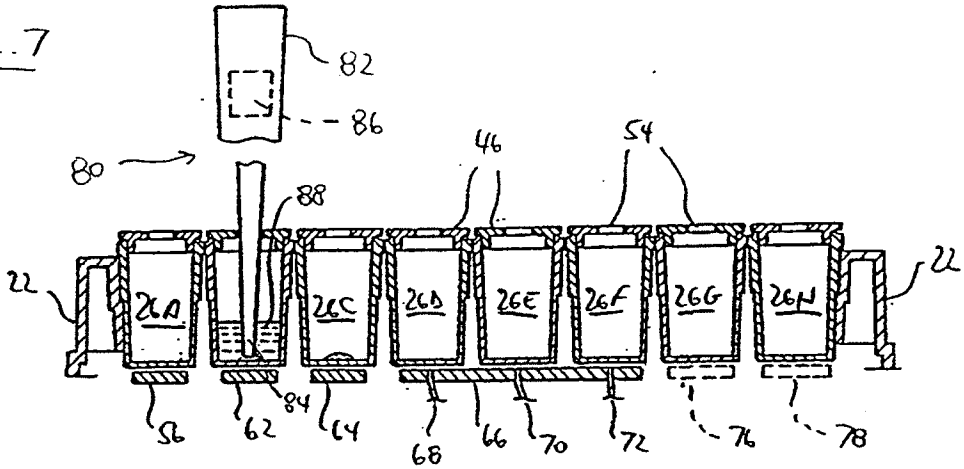

FIG. 8

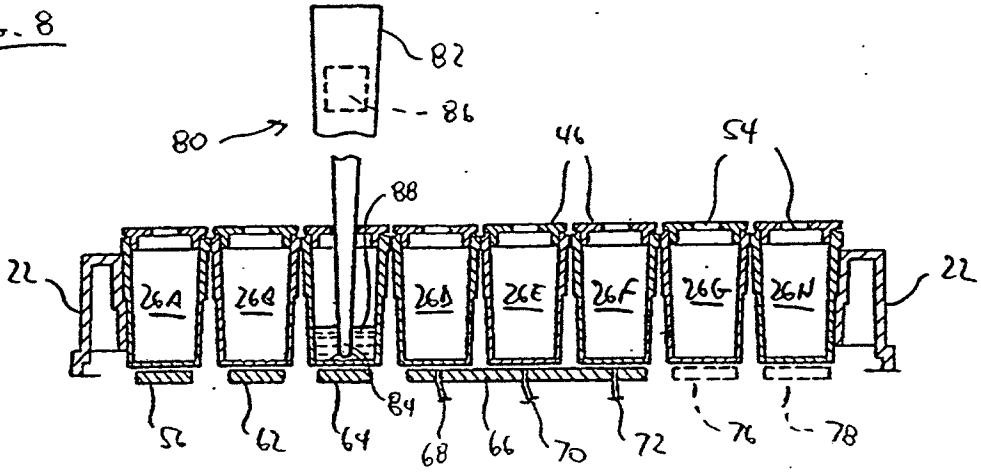

FIG. 9

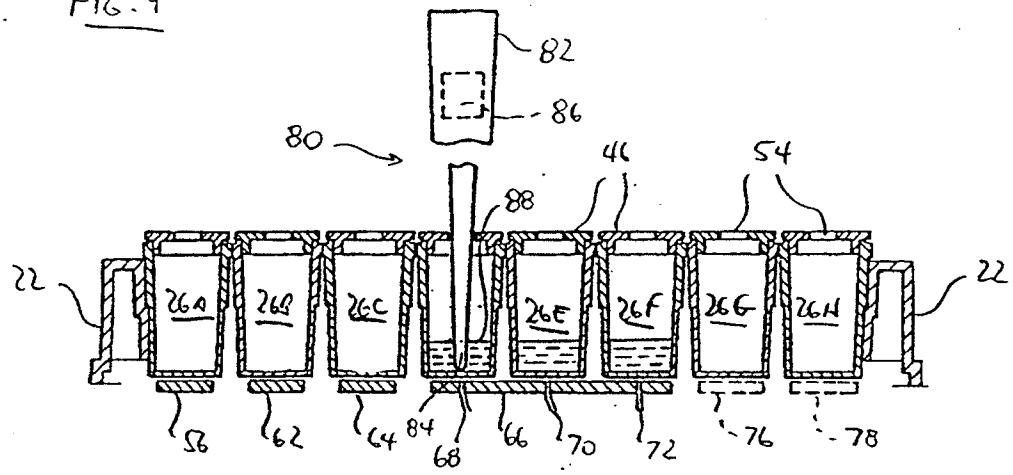

FIG. 10

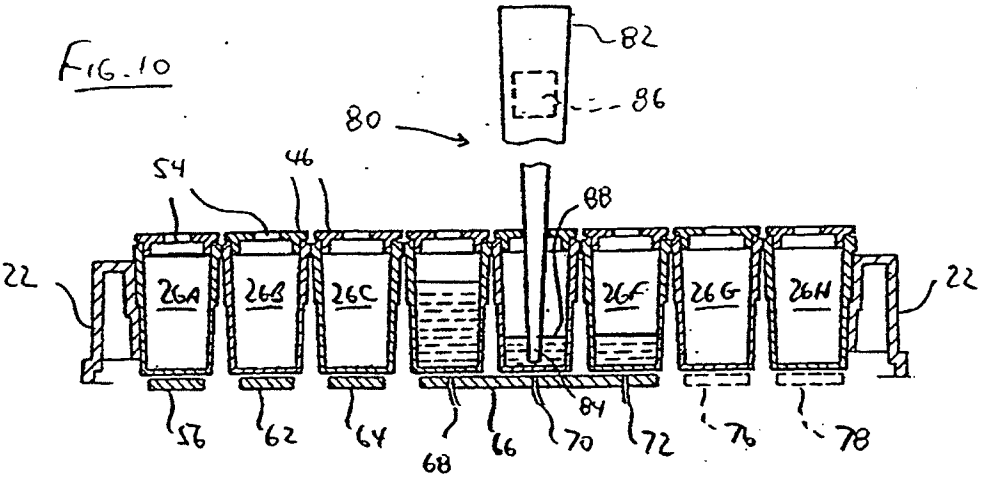

FIG. 11

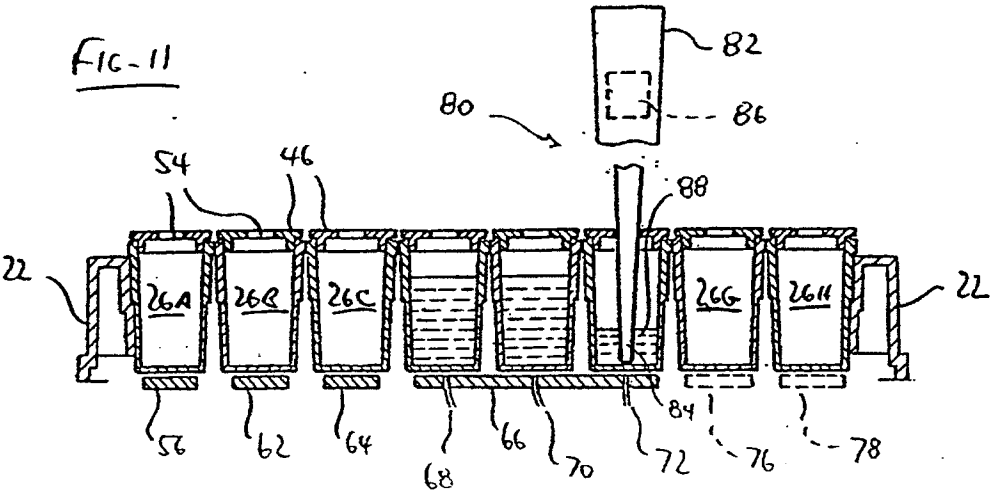

FIG. 12

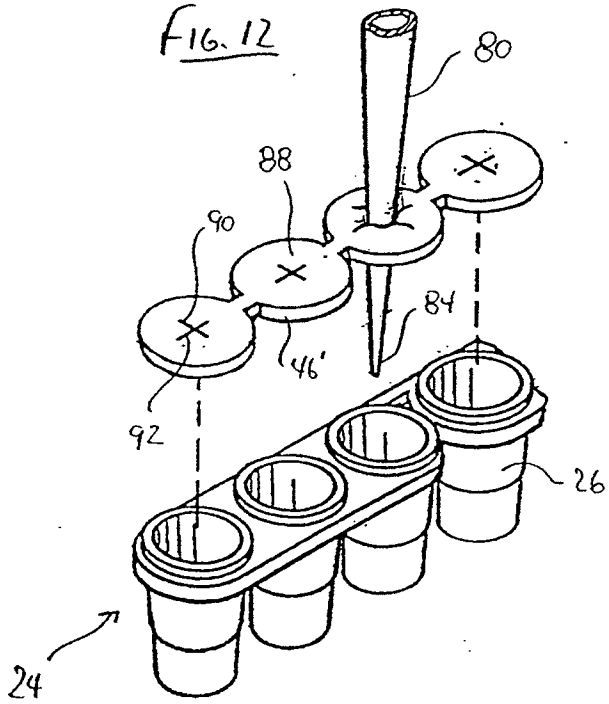

FIG. 13

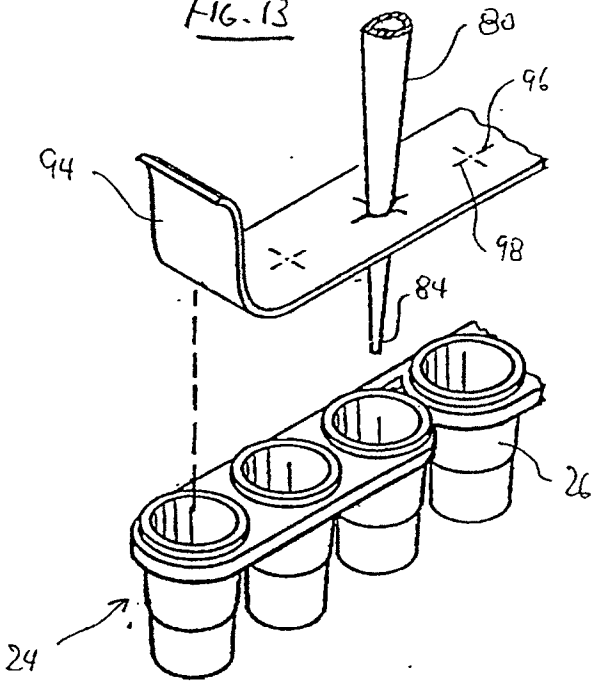

FIG. 14

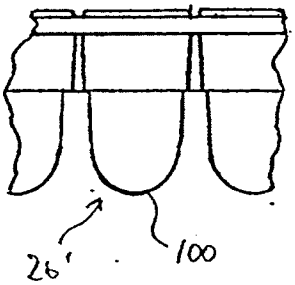

FIG. 15

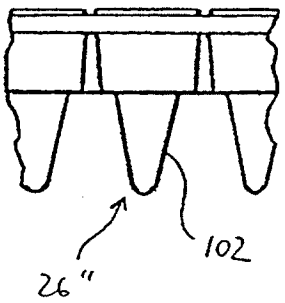

FIG. 16